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Low Prevalence of Anti-Hepatitis C Virus Antibodies in Female Hemodialysis Patients Without Blood Transfusion: A Multicenter Analysis

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To investigate whether nosocomial infection with hepatitis C virus (HCV) in chronic hemodialysis patients is related primarily to hemodialysis procedures, a multicenter analysis was carried out on 2,132 chronic hemodialysis patients (male: 1,274, female: 858) from 23 dialysis units using a second-generation anti-HCV antibody assay. The prevalence of anti-HCV antibodies in patients with blood transfusion (29.9%) was significantly higher ($P < .0001$) than in those without blood transfusion (7.6%). Although the prevalence of anti-HCV antibodies increased with the length of hemodialysis in males without blood transfusion, it did not increase even after long-term hemodialysis (more than 5 years) in females without blood transfusion, who exhibited a rate (1.9%) similar to that of healthy blood donors in Japan. There was a significant correlation between the presence of anti-HCV antibodies and anti-HBs antibody in males without blood transfusion. In anti-HBs antibody–negative male patients without blood transfusion, the prevalence of anti-HCV antibodies was significantly lower compared with anti-HBs antibody–positive male patients without blood transfusion. There was marked difference in the prevalence rate in patients without blood transfusion among dialysis units, and there was no correlation between the prevalence and the mean period of dialysis of each dialysis unit. Although nosocomial infection with HCV appears to be related to the hemodialysis environment, the low prevalence of anti-HCV antibodies in females suggests that dialysis procedures per se may not present the risk of hepatitis C virus infection.

KEY WORDS: epidemiology, hepatitis C virus, infection, sex difference

INTRODUCTION

The incidence of viral hepatitis B in chronic hemodialysis patients has been decreased by improvements in infection control strategy [Alter et al., 1986]. Nevertheless, liver disease is one of the most important causes of morbidity and mortality in hemodialysis patients. Non-A, non-B hepatitis appears to be the major cause of liver dysfunction in these patients, and this is now shown to be due to hepatitis C virus (HCV) infection [Choo et al., 1989]. Many reports on the prevalence of HCV infection in hemodialysis patients have been published [Gilli et al., 1990; Zeldis et al., 1990; Chan et al., 1993; Davis et al., 1994] since assays for HCV infection were first developed [Kuo et al., 1989]. Although it is generally accepted that the prevalence of HCV infection is higher in chronic hemodialysis patients than in the normal population, there is considerable difference in the prevalence rate among dialysis centers. Rates range from 10% to 50% using the first-generation anti-HCV antibody assay, and even higher rates have been reported using the second-generation assay [Davis et al., 1994].

Although a past history of blood transfusion has been shown to be one of the risk factors for HCV infection in these patients, HCV transmission other than by blood transfusion has been suggested. Irie et al. [1994] reported recently that the prevalence of anti-HCV antibodies was closely related to the duration of hemodialysis and was high even in hemodialysis patients without a history of blood transfusion, thus suggesting nosocomial infection. More recently, molecular evidence of nosocomial infection with HCV in dialysis units has been reported [Allander et al., 1994; Sampietro et al., 1995]. It is not known, however, whether nosocomial infection with HCV in chronic hemodialysis patients is related primarily to hemodialysis procedures.

In the present study, a multicenter analysis was undertaken to clarify the role of factors other than blood transfusion in HCV transmission in chronic hemodialysis patients.

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TABLE I. Clinical Characteristics of the 2,132 Hemodialysis Patients From 23 Dialysis Units†

	History of blood transfusion		
	+	−	Total
Number of patients	1,076	1,056	2,132
Sex (male/female)	582/494	692/364	1,274/858
Prevalence of anti-HCV (%)	29.9*	7.6	19.7
Age (years)	56.3 ± 12.7 (19–87)	56.1 ± 13.5 (17–89)	56.2 ± 13.0 (17–89)
Duration of hemodialysis (years)	7.8 ± 5.6* (0.5–26)	4.7 ± 4.3 (0.5–21)	6.3 ± 5.2 (0.5–26)
AST (U/l)	17 ± 12	15 ± 10	16 ± 11
ALT (U/l)	15 ± 12	13 ± 13	14 ± 13

†Values are expressed as mean ± SD. Figures in parentheses represent the range of the values. Values of AST and ALT were obtained from patients who were negative for serum hepatitis B s antigen (1,049 with blood transfusion, 1,048 without blood transfusion). AST, aspartate aminotransferase; ALT, alanine aminotransferase.
*$P < .0001$ compared with the group without blood transfusion.

MATERIALS AND METHODS

Two thousand one hundred ninety-six patients in 23 dialysis units around the greater Tokyo area were screened. Thirty-two of these patients were excluded because data with second generation anti-HCV antibody assays were not available, and another 32 patients were excluded because no information on history of blood transfusion could be obtained. After the screening, 2,132 patients (male: 1,274, female: 858) were enrolled in the present study. These patients were not homosexuals or drug abusers, and they had not received renal transplantation or immunosuppressive agents for autoimmune diseases. A history of blood transfusion was recorded. Anti-HCV antibody screening of blood trans fusion was started in November 1989 in Japan. Serum anti-HCV antibodies and anti-HBs antibody were deter mined using a second-generation anti-HCV antibody assay (Abbott RIA kit, Abbott Laboratories, North Chicago, IL; or the Ortho EIA kit, Ortho Diagnostic Systems, Raritan, NJ) and anti-HBs assay (Abbott RIA kits), respectively. Serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured by a multichannel autoanalyzer in hemodialysis patients who were negative for hepatitis B surface antigen.

Statistical significance was determined by the chi-square test and correlation analysis using Statview II (Abacus Concepts, Inc., Berkeley, CA). A multivariate analysis was carried out using JMP (SAS Institute Inc., Gary, NC). *P* values less than .05 were considered statistically significant.

RESULTS

Characteristics of the patients are summarized in Table I. The prevalence of anti-HCV antibodies was 29.9% in chronic hemodialysis patients with blood transfusion and 7.6% in those without blood transfusion (Table I). No difference was observed in serum levels of AST and ALT between these two groups. The relationship between patient age and the presence of the antibodies is shown in Table II. Although no difference was observed in the prevalence of anti-HCV antibodies among three age groups with blood transfusion, the positivity rate in groups without blood transfusion was significantly higher in those above 50 years. There was no correlation between average lengths of hemodialysis and ages in patients who had no history of blood transfusion. Among the male patients without blood transfusion, the prevalence of anti-HCV antibodies was significantly higher in anti-HBs–positive patients than in anti-HBs–negative patients (Table III). Although a similar tendency was observed in female patients, the data were not significantly different. Even in anti-HBs–negative patients, the prevalence was higher in males than in females, who maintained rather a low positivity rate (3.1%). The prevalence of anti-HCV antibodies increased with the length of hemodialysis in both males and females with blood transfusion (Table IV). In patients without blood transfusion, the prevalence was correlated with the length of hemodialysis in males, whereas it did not increase even after long-term hemodialysis (more than 5 years) in females, a group who exhibited a rate similar to that of healthy blood donors in Japan [Tanaka et al., 1995] (Table II). A multivariate analysis of patients without blood transfusion showed that age, status of anti-HBs antibody, and length of hemodialysis were independent risk factors for the positivity of anti-HCV antibodies in male patients (Table V). These factors were not significant in female patients.

The ranges in the prevalence of anti-HCV antibodies in hemodialysis patients without blood transfusion varied among dialysis units. The rate did not correlate with the mean length of hemodialysis of respective units ($r = 0.075$, not significant).

DISCUSSION

High prevalence rates of HCV infection attributed mainly to blood transfusion have already been reported in chronic hemodialysis patients. In the present study, a high prevalence of anti-HCV antibodies (29.9%) was

TABLE II. The Prevalence of Anti-HCV Antibodies in Hemodialysis Patients as Assessed by Age†

	Age (years)		
	<30	30–50	>50
Blood transfusion (+)	26.1 (6/23)	31.3* (109/348)	29.3* (206/704)
Blood transfusion (−)	6.1 (2/33)	4.0 (13/329)	9.4** (65/694)
Males	7.7 (2/26)	5.3 (12/225)	12.5**,*** (55/441)
Females	0 (0/7)	1.0 (1/104)	4.0 (10/253)
Normal population in Japan[a]			
Males	0.34	1.14	4.31
Females	0.34	0.92	5.16

†Values are expressed as percentages. Figures in parentheses represent the no. of patients studied in respective groups.
[a]Adopted from data based on 192,978 individuals [Tanaka et al., 1995].
*$P < .0001$ compared with respective values without blood transfusion.
**$P < .01$ compared with those aged 30 to 50 years.
***$P < .001$ compared with females without blood transfusion.

TABLE III. The Prevalence of Anti-HCV in Relation to Anti-HBs Antibody Status in Hemodialysis Patients†

	Anti-HBs antibody			
	Positive		Negative	
	Males	Females	Males	Females
Blood transfusion (+)	37.5* (42/112)	39.6* (44/111)	31.4* (91/290)	26.5* (66/249)
Blood transfusion (−)	16.5** (15/91)	8.1 (3/37)	8.4*** (37/443)	3.1 (7/229)

†Values are expressed as percentages. Figures in parentheses represent the no. of patients studied in the respective groups. Patients who were positive for serum HBs Ag were excluded (N = 39).
*$P < .001$ compared with respective groups without blood transfusion.
**$P < .05$ compared with respective anti-HBs–negative patients.
***$P < .01$ compared with females without blood transfusion.

TABLE IV. The Prevalence of Anti-HCV Antibodies in Hemodialysis Patients as Assessed by the Length of Hemodialysis†

	Hemodialysis period (years)					
	≤5		>5		Total	
	Males	Females	Males	Females	Males	Females
Blood transfusion (+)	24.1** (62/257)	13.2 (26/197)	36.5*** (118/323)	38.7*** (115/297)	31.0* (180/580)	28.5* (141/494)
Blood transfusion (−)	7.6** (35/461)	3.5 (9/254)	14.5**,*** (33/227)	1.9 (2/107)	9.9** (68/688)	3.0 (11/361)

†Values are expressed as percentages. Figures in parentheses represent the no. of patients studied in respective groups.
*$P < .0001$ compared with respective values without blood transfusion.
**$P < .05$ compared with respective females.
***$P < .01$ compared with respective groups with on hemodialysis for less than 5 years.

found in patients with a history of blood transfusion, and a much lower prevalence (7.6%) in those without a history of blood transfusion. The present findings are in agreement with previous observations.

To date, however, there are no reports on sex difference in the prevalence of anti-HCV antibodies in chronic hemodialysis patients. In the present study, it was shown that the prevalence of anti-HCV antibodies did not increase even after long-term hemodialysis (more than 5 years) in female patients without blood transfusion, a group that exhibited a rate similar to that seen in normal populations in Japan [Tanaka et al., 1995]. On the other hand, the prevalence in males without a history of blood transfusion was still higher than that in comparable healthy individuals [Tanaka et al., 1995]. Therefore, hemodialysis without blood transfusion may not increase the risk of HCV infection in females. Study of sex difference was probably omitted in previous reports because of the relatively small numbers of patients. It is unlikely that female patients eliminated HCV more easily than male patients to yield reverse-seroconversion in anti-HCV antibody status, because there were no sex differences in the prevalence rate of anti-HCV antibodies between females and males who had a history of blood

TABLE V. Multiple Logistic Estimates of Risk Factors for Anti-HCV Antibodies in Hemodialysis Patients Without Blood Transfusion*

	Parameter estimate	Standard error	WALD chi-square	Odds ratio	95% Confidence interval		P value
Males							
Intercept	−2.5801	0.3004	73.7500	—	—		—
Age (1–0)	0.9660	0.3166	9.3100	2.6273	1.4125,	4.8870	0.0023
Anti-HBs (1–0)	0.3250	0.1621	4.0200	1.3906	1,0047,	1.9247	0.0450
Hemodialysis (1–0)	0.4247	0.1311	10.4900	1.5424	1.1854,	2.0068	0.0012
Females							
Intercept	−5.7486	2.0741	8.0000	—	—		—
Age (1–0)	1.4357	1.0590	1.8400	4.2025	0.5055	34.9424	0.1752
Anti-HBs (1–0)	0.5749	0.3538	2.6400	1.7770	0.8757	3.6056	0.1042
Hemodialysis (1–0)	−0.3199	0.3975	0.6500	0.7262	0.3279	1.6082	0.4209

*Age (1 = more than 50 years, 0 = 50 years or less); anti-HBs antibody (1 = positive, 0 = negative); hemodialysis (1 = more than 5 years, 0 = 5 years or less).

transfusion. Furthermore, female patients who had eliminated HCV would be infected with HCV again with an equal opportunity, since re-infection even with the same strain of HCV has been shown to occur [Farci et al., 1992].

In male patients without blood transfusion, the prevalence of HCV infection increased with the length of hemodialysis. This suggested that HCV infection through pathways other than blood transfusion exists, although it is also possible that HCV infection itself was the cause of membranoproliferative glomerulonephritis [Johnson et al., 1993] that might lead to renal insufficiency. In the present study, the prevalence of anti-HCV antibodies in males without blood transfusion was related significantly to the presence of anti-HBs antibody, and the rate was high even if they were negative for anti-HBs antibody. The results suggest that male patients might have more chance of being exposed to HCV through pathways other than blood transfusion than female patients.

Molecular analyses have shown that nosocomial transmission does exist in chronic hemodialysis patients. It is a matter of controversy, however, whether the transmission mainly occurs through the dialysis procedures themselves. The difference in the prevalence of anti-HCV antibodies between males and females in the present study suggests that dialysis procedures per se are not likely to be the sole cause of the high prevalence of HCV infection in patients without blood transfusion. In fact, there was a variety of ranges in the prevalence of anti-HCV antibodies in hemodialysis patients without blood transfusion among dialysis units. The prevalence did not relate with the mean length of hemodialysis periods of dialysis of respective units. The results suggest that although nosocomial transmission of HCV is possible in the hemodialysis environment, iatrogenic transmission from sources other than dialysis itself seems to exist, and careful infection control measures are necessary in dialysis units where high prevalence rates of HCV infection are reported in patients without a history of blood transfusion. Alternatively, male dialysis patients might have a greater chance of infection with HCV not related to dialysis, or they might be more susceptible to HCV infection.

Because of the large number of patients in the present study, anti-HCV antibodies were measured for the detection of HCV infection. It has been shown that there is discrepancy between anti-HCV antibody assay and HCV-RNA determination in hemodialysis patients, and some patients are positive for anti-HCV antibodies but negative for HCV-RNA [Sakamoto et al., 1993]. These patients seem to have been infected previously with HCV without ongoing infection. Since the present study was designed to investigate the rate of infection in chronic hemodialysis patients rather than the effect of ongoing infection, the analysis of anti-HCV antibodies appears to be adequate.

In conclusion, the prevalence of anti-HCV antibodies differs between males and females in chronic hemodialysis patients without blood transfusion, suggesting that HCV transmission through pathways other than hemodialysis exists. Although nosocomial infection of HCV appears to be related to the hemodialysis environment, the low prevalence of anti-HCV antibodies in females suggests that procedures of hemodialysis per se may not be the risk for hepatitis C virus infection.

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